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Electrochemical Difluoromethylation of Electron-Deficient Alkenes

He-Huan Xu, Jinshuai Song and Hai-Chao Xu*

Abstract: Electrochemical 1,2-hydroxydifluoromethylation and C–H difluoromethylation of acrylamides have been developed using CF₂HSO₂NHNHBoc as the source of CF₂H group. These electricity-powered oxidative alkene functionalization reactions do not need transition metal catalysts and chemical oxidants. The reaction outcome, 1,2-difuntionalization or C–H functionalization, is determined by the substituents on the amide nitrogen atom of the acrylamides instead of reaction conditions.

Alkene functionalization reactions such as the vicinal difunctionalization^[1] and olefinic C-H functionalization^[2] are important synthetic methods that have been under constant investigation. We have recently reported a one-step synthesis of an easily handled difluoromethylation reagent CF₂HSO₂NHNHBoc (1) and applied this reagent in radical difluoromethylation of alkynes and alkenes.^[3] With our continued interest in applying compound 1 in the synthesis of CF₂Hcontaining organofluorine compounds, we envision alkene 1,2hydroxydifluoromethylation and C-H difluoromethylation via radical-polar crossover reaction (Scheme 1a).^[4] Although several C-H trifluoromethylation reactions of alkenes have been disclosed,^[5] the analogous difluoromethylation have remained elusive. On the other hand, radical-polar crossover strategy has been employed in photochemical 1,2-hydroxydifluoromethylation of electron-rich aryl alkenes using an [Ir]-catalyst and electrophilic difluoromethylation reagents (Scheme 2b).[4a,b] However, application of such a mechanistic manifold in functionalization of electron-deficient alkenes has remained to be challenging because of the unfavored oxidation of the electron-deficient carbon radical to the corresponding carbocation.[4k,6]

Organic electrochemistry is a green and enabling synthetic tool and has been gaining increasing traction.^[7] Particularly, the anode is a powerful electron sink and has been employed for achieving difficult oxidation reactions.^[8,9] We have been interested in the development of electrochemical methods to promote oxidative radical reactions.^[3,10] Herein we report electrochemical 1,2-hydroxydifluoromethylation and C–H difluoromethylation of acrylamides using reagent 1 as CF₂H source. No transition metal catalyts or chemical oxidants are needed for these electricity-powered reactions.

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Scheme 1. Difluoromethylation of alkenes.

We began our study by optimizing the electrolysis conditions for the 1,2-hydroxydifluoromethylation of acrylamide 2 using reagent 1 and H₂O as the reagents (Tables 1). Our previously developed electrocatalytic conditions employing ferrocene as the redox catalyst did not work for the current reaction probably because of the relatively low oxidation potential of ferrocene.^[3] Further studies employed direct electrolysis in a three-necked round-bottomed flask equipped with a reticulated vitreous carbon (RVC) anode and a Pt plate cathode. The optimal conditions involved electrolysis at 70 °C using a constant current of 10 mA in a mixed solvent of acetone/H₂O (1:2). Under these conditions, the desired product 3 was isolated in 72% yield (entry 1). H₂O was essential for the success of the reaction as its absence resulted in no formation of 3 (entry 2). Reduction of the concentration of H₂O led to reduced current efficiency (entries 3 and 4). Replacing acetone with 2,2,2-trifluoroethanol (TFE) also led to yield reduction (entry 5). When the reaction was carried out at RT instead of 70 °C, product 3 was not formed and the amide 1 was recovered in 84% (entry 6). Heating was needed to increase the solubility of the organic reactants in the aqueous solution. Other anode materials such as graphite plate (entry 7) and glassy carbon plate (entry 8) were inefficient in promoting the formation of 3 than RVC. The electrochemical alkene difunctionalization reaction could be carried out on gram scale with efficiency similar to the mini gram scale reaction (entry 9).

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Table 1. Optimization of reaction conditions.[a]

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Entry	Deviation from standard conditions	Yield [%] ^[b]
1	none	72 ^[c]
2	no H ₂ O	0 (40)
3	acetone/H ₂ O (2:1) as solvent	6 (75)
4	acetone/H ₂ O (1:1.5) as solvent	69 ^[c,d]
5	TFE/H ₂ O (1:2) as solvent	45 ^[c]
6	reaction at RT	0 (84)
7	graphite plate (1 cm x 1 cm)	8 (59)
8	glass carbon plate (1 cm x 1 cm)	0 (82)
9	1.0 g (4.5 mmol) of 2	69 [0.91 g]

[a] Reaction conditions: RVC anode (1 cm x 1 cm x 1.2 cm), Pt cathode (1 cm x 1 cm), **2** (0.2 mmol), **1** (0.4 mmol), solvent (6 mL), argon, $j_{anode} \ge 0.1$ mA cm⁻², 2.0 h (3.7 F mol⁻¹ based on **2**). [b] Yield determined by ¹H-NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Unreacted **2** in parenthesis. [c] Isolated yield. [d] Reaction time = 2.8 h.

We then investigated the substrate scope of the alkene difunctionalization reaction by varying the substituents of R¹ on the alkene and R² on the amide nitrogen atom (Scheme 2). The phenyl ring on the alkene could be substituted at the para position with electron donating OMe (4) and halogens such as CI (5) and Br (6 and 8), but not the highly electron-withdrawing acetyl group (7). Many other arvl groups such as 1-naphthyl (9). 3-pyridyl (10) and 2-thiophenyl (11) were tolerated at R¹ position but not a Me group (12). Phenyl groups bearing substituents with diverse electronic properties such as OMe (13), F (14), Cl (15), CF_3 (16), CN (17), and ester (18) were suitable as R^2 on the amide nitrogen. Besides the secondary N-aryl amides, a primaryl amide also afforded the hydroxydifluoromethylation product in 50% yield (20). However, a secondary amide bearing a N-Me group underwent decomposition and failed to afford the alkene difunctionalization product 21. While an ester reacted to afford the difunctionalization product (22) in moderate yield (38%), the corresponding free carboxylic acid failed completely (23). Hydroxytrifluoromethylation could also be achieved using $CF_3SO_2NHNHBoc^{[11]}$ as the CF_3 source (24).

Further investigations revealed that tertiary amides underwent C–H difluoromethylation to give CF₂H-substituted acrylamines instead of alkene difunctionalization (Scheme 3). The C–H difluoromethylation reactions were best carried out in TFE/H₂O (5:1) with Et₄NOTs as the electrolyte (Table S1). Under these conditions, tertiary acrylamides with different Nsubstituents reacted to afford the desired products with generally good yields and stereoselectivity (25–28). The stereochemistry of the alkene product was determined using nuclear Overhauser effect (NOE) experiment. Once again, the use of CF₃SO₂NHNHBoc instead of **1** led to the formation of CF₃-containing product **29** in 97% yield.^[5]



Scheme 2. Scope of pyrrolidine synthesis. Reaction conditions: Table 1, entry 1, 1.3–3.6 h (2.4–6.7 F mol⁻¹). [a] Reaction in MeCN/H₂O (2 mL/4 mL). [b] Reaction in TFE/H₂O (5 mL/1 mL).



Scheme 3. Scope of C–H difluoromethylation reaction. Reaction conditions: acrylamide (0.2 mmol), TFE (5 mL), H_2O (1 mL), 3.2–5 h (5.9–9.3 F mol⁻¹). [a] Determined by ¹H NMR analysis of crude reaction mixture.

a) Structure-reactivity relationship



b) ¹⁸O-labelling experiment



Scheme 4. Mechanistic studies.



Scheme 5. Mechanistic proposal and rationale. a) Mechanistic proposal. b) Possible equilibrium of α -amide cation **III**_A with aza-oxyallyl cation **IV**. c) Rationale for the *Z*-selective proton elimination.

The electrolysis of acrylamide **2** under the conditions optimized for olefinic C–H difluoromethylation afforded **3** and **30** in 32% and 2% yield, respectively. In addition, the reaction of tertiary acrylamide **31** under the conditions optimized for alkene difunctionalization furnished the C–H functionalization product **25** as the only identifiable product in 63% yield. These results suggested that the reaction outcome of the acrylamides was determined by the substitution patterns on the amide nitrogen

atom instead of the reaction parameters. The difunctionalization of **2** in the presence of H₂¹⁸O afforded [¹⁸O]-**3** in 40% yield (79% ¹⁸O).^[12] Dehydration of [¹⁸O]-**3** afforded **30** in 50% yield. These experiments suggested that the hydroxyl group in compound **3** was originated from H₂O.

А possible mechanism for the electrochemical difluoromethylation reaction has been proposed (Scheme 5a). Anodic oxidation of the reagent 1 on the anode produces diazene I, which undergoes decomposition to generate difluoromethyl radical (•CF2H).[3] Radical addition to the acrylamide followed by one-electron oxidation at the anode furnishes the α -carbonyl carbocation II. The Ar¹ group, which can stabilize the carbocation, is critical for the oxidation of the electron-deficient carbon radical I. Depending on the substituents on the amide nitrogen atom, the carbocation II either reacts with H₂O to afford the alkene difunctionalization product or undergoes proton elimination to give the C-H functionalization product. The carbocation IIIA bearing а secondary amide moiety probably exists in equilibrium with the aza-oxyallyl cation IV, which is known to favor addition reaction over proton elimination (Scheme 5b).^[13] The proton elimination reaction of IIIB proceed via the conformation IIIB1 instead of the more sterically encumbered IIIB2 affording the Z-isomer as the major product (Scheme 5c).

In summary, we have developed electrochemical difluoromethylation reactions of acrylamides using CF₂HSO₂NHNHBoc as the difluoromethylation reagent. While secondary N-aryl acrylamides react to afford α -hydroxy amides via alkene hydroxydifluoromethylation, tertiary acrylamides undergo olefinic C–H functionalization.

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Keywords: electrosynthesis • alkene difunctionalization • difluoromethylation • radicals • C–H functionalization

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